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***Supplementary Table 1. Class I Mutations Identified In Study Cohort.***

| ID | Mutation | | Mutation Effect | Exon | Domain | Rate | Ref. |
|---|---|---|---|---|---|---|---|
| | cDNA | Protein | | | | | |
| ***PKD1* gene** | | | | | | | |
| **Frameshift:** | | | | | | | |
| JHU111 | 559delTTTAA | N116fsX | Stop Codon at 117 | 3 | LRR2 | 1/164 | N |
| JHU568 | 1124insCT | W305 fsX | Stop Codon at 334 | 5 | PKDR1 | 1/164 | N |
| JHU582 | 2291ins1 | P694 fsX | Stop Codon at 713 | 10 | | 1/164 | N |
| JHU585 | 2297ins1 | A696 fsX | Stop Codon at 713 | 10 | | 1/164 | N |
| JHU15 | 5225delAG | R1672 fsX | Stop Codon at 1721 | 15 | PKDR11 | 1/164 | [1-3] |
| JHU508 | 5365insT | V1718 fsX | Stop Codon at 1770 | 15 | PKDR12 | 1/164 | N |
| JHU613 | 6666insG | D2152 fsX | Stop Codon at 2174 | 15 | REJ | 1/164 | N |
| JHU611 | 6881insA | P2224 fsX | Stop Codon at 2261 | 15 | REJ | 1/164 | N |
| JHU577 | 8713delT | F2834 fsX | Stop Codon at 2874 | 23 | | 1/164 | N |
| JHU600 | 9134ins1 | P2975 fsX | Stop Codon at 3068 | 24 | | 1/164 | N |
| JHU579 | 9536ins5 | I3109 fsX | Stop Codon at 3317 | 26 | | 2/164 | N |
| JHU609 | 9536ins5 | I3109 fsX | Stop Codon at 3317 | 26 | | 2/164 | N |
| JHU599 | 10239delT | L3343 fsX | Stop Codon at 3395 | 30 | TM3 | 1/164 | N |
| JHU104 | 11587delG | G3792 fsX | Stop Codon at 3824 | 40 | | 1/164 | [4] |
| **Nonsense:** | | | | | | | |
| JHU605 | 483 C>A | S91X | Stop Codon at 91 | 2 | LRR1 | 1/164 | N |
| JHU567 | 4517 C>T | R1436X | Stop Codon at 1436 | 15 | PKDR8 | 1/164 | N |
| JHU108 | 7006 C>A | Y2265X | Stop Codon at 2265 | 15 | REJ | 1/164 | N |
| JHU563 | 7499 C>T | R2430X | Stop Codon at 2430 | 18 | REJ | 1/164 | [5, 6] |
| JHU593 | 7877 C>T | Q2556X | Stop Codon at 2556 | 19 | REJ | 1/164 | [7] |
| JHU083 | 8267 C>T | Q2686X | Stop Codon at 2686 | 22 | REJ | 1/164 | N |
| JHU574 | 8639 G>T | E2810X | Stop Codon at 2810 | 23 | REJ | 1/164 | N |
| JHU620 | 12243 G>A | W4011X | Stop Codon at 4011 | 44 | TM9 | 1/164 | N |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Splicing:** | | | | | | | |
| JHU572 | | IVS4+1G>A. | Loss of donor site | 4 | | 1/164 | N. |
| JHU580 | | IVS19+1G>T. | Loss of donor site | 19 | REJ | 1/164 | N. |
| ***PKD2* gene** | | | | | | | |
| **Frameshift:** | | | | | | | |
| JHU586 | 2226insA | 720fsX | Stop Codon at 730 | 11 | | 2/164 | N |
| JHU116 | 2226insA | 720fsX | Stop Codon at 730 | 11 | | 2/164 | N |
| JHU591 | 2422delAG | 786fsX | Stop Codon at 793 | 12 | CC | 1/164 | N |
| **Nonsense:** | | | | | | | |
| JHU578 | 982 C>T | R306X | Stop Codon at 360 | 4 | TM1 | 2/164 | [8] |
| JHU583 | 982 C>T | R306X | Stop Codon at 360 | 4 | TM1 | 2/164 | [8] |
| JHU607 | 2224 C>T | R742X | Stop Codon at 742 | 11 | | 1/164 | [9] |
| JHU594 | 2680C>T | R872X | Stop Codon at 872 | 14 | | 3/164 | [10] |
| JHU566 | 2680C>T | R872X | Stop Codon at 872 | 14 | | 3/164 | [10] |
| JHU608 | 2680C>T | R872X | Stop Codon at 872 | 14 | | 3/164 | [10] |
| **Splicing:** | | | | | | | |
| JHU562 | | IVS7-1G>A | Loss of acceptor site | 7 | | 1/164 | N |

Rate=the number of times that the variant was observed in the study population (N=82, 164 chromosomes). Leucine Rich Repeat (LRR), Polycystic Kidney Disease Repeat # (PKD-R), Receptor for Egg Jelly domain (REJ), Transmembrane (TM), Coiled Coil (CC), Novel change, identified in this study (N).

***Supplementary Table 2. Analysis Of Splice Site Mutations.***

| | | | SSPNN | | | ASSA | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ID | Mutation | Intron | Initial Score | Final Score | Mutation Effect | Initial (Ri) | Final (Ri) | Fold Change | % Binding (Ri/Rf) | Mutation Effect | PKDx Class. | Rate | Ref. |
| ***PKD1* gene** | | | | | | | | | | | | | |
| JHU572 | IVS4+1G>A | 4 | 0.97 | N/A | Site abolished | 9.5 | -3.4 | -699.5 | N/A | Site abolished | Class I | 1/164 | N |
| JHU411 | IVS10-4G>A | 10 | 0.62 | 0.98 | Strengthened | 12.9 | 13 | 1.1 | 109.6 | Strengthened | Polymorphism | 1/164 | N |
| JHU580 | IVS19+1G>T | 19 | 1 | N/A | Site abolished | 10.7 | 2.9 | -223.6 | N/A | Site abolished | Class I | 1/164 | N |
| JHU617 | IVS20-16C>G | 16 | 0.71 | 0.71 | No change | 3.4 | 3.4 | 1 | 100 | No change | Polymorphism | 1/164 | N |
| JHU573 | IVS24+5G>C | 24 | 0.91 | N/A | Site abolished | 6.9 | 3 | -15.5 | 6.4 | Leaky site | Class II | 2/164 | N |
| JHU595 | IVS24+5G>C | 24 | 0.91 | N/A | Site abolished | 6.9 | 3 | -15.5 | 6.4 | Leaky site | Class II | 2/164 | N |
| JHU590 | IVS24+28G>T | 37 | N/A | 0.63 | Site created | -1.1 | 7.1 | 138.4 | 13839.8 | Site created | Class II | 1/164 | N |
| JHU569 | IVS26+76C>A | 26 | 0.69 | 0.69 | No change | 5.6 | 5.8 | 1.2 | 115.9 | Strengthened | Polymorphism | 1/164 | N |
| JHU601 | IVS37-4C>T | 37 | 0.99 | 0.99 | No change | 4.9 | 4.9 | 0 | 100 | No change | Polymorphism | 1/164 | N |
| JHU604 | IVS37-10C>A | 37 | 0.89 | N/A | Site abolished | 4.9 | 2.9 | -4.1 | 24.5 | Leaky site | Class II | 1/164 | [4] |
| ***PKD2* gene** | | | | | | | | | | | | | |
| JHU559 | IVS6-4C>T | 6 | 0.92 | 0.92 | No change | 7.8 | 8.1 | 1.2 | 121.4 | Strengthened | Polymorphism | 1/164 | N |
| JHU562 | IVS7-1G>A | 7 | 1 | N/A | Site abolished | 6.3 | -1.3 | -77.5 | N/A | Site abolished | Class I | 1/164 | N |
| JHU105 | IVS8+5G>A | 8 | 0.83 | N/A | Site abolished | 7.8 | 4.3 | -11.5 | 8.7 | Leaky site | Class II | 1/164 | N |

Intronic changes were analyzed using the splice site prediction programs SSPNN and ASSA (see text). Class I variants directly affect consensus splice donor/acceptor sites. As expected both programs predict that these changes will abolish splicing. Class II mutations are intronic changes that do not involve canonical splice sites but which are nonetheless predicted by both programs to alter the native splicing pattern. Initial (Ri): initial information content measured at the base before a mutation is made. Final (Ri): final information content measured at the base after a mutation is made. Fold change indicates the change in binding affinity of the two sites. Percent (%) Binding (Final/Initial), indicates the change of binding energy calculated as a percentage. If there is no change at the splice site then the fold change is 1.0. A positive fold change indicates that a new site is created while a negative change signifies that the site is abolished. (N), novel, variant identified in this study. Rate=the number of times that the variant was observed in the study population (N=82, 164 chromosomes).

***Supplementary Table 3. Class II Mutations: In Frame Deletions/Insertions.***

| ID | Mutation | | Exon | Domain | Conservation | | | | Rate | Ref |
|---|---|---|---|---|---|---|---|---|---|---|
| | cDNA | Protein | | | *Fr* | *Mm* | *Hs* | LC | | |
| ***PKD1* gene** | | | | | | | | | | |
| JHU115 | 514-551delCAA | N101del | 3 | LRR2 | N | N | N | FC | 1/164 | N |
| JHU107 | 1848-1851delTGG | V546del | 8 | | V | V | V | FC | 1/164 | N |
| JHU560 | 8892-8898del CCAACTCCG | ANS2894del | 23 | | AGA | VGS | ANS | HC | 1/164 | N |
| JHU592 | 9905-9909delAAG | K3232del | 28 | PLAT | I | K | K | HC | 1/164 | N |
| JHU571 | 10070-10074delCTC | L3287del | 29 | TM2 | L | L | L | FC | 1/164 | N |
| JHU112 | 12597-12600delTGG | V4129del | 45 | | V | V | V | FC | 1/164 | N |
| ***PKD2* gene** | | | | | | | | | | |
| JHU596 | 374-378insTGG | 103insV | 1 | Poly-Glu | - | V | V | HC | 1/164 | N |
| JHU416 | 1879-1882delTTC | F605del | 8 | TM5 | - | F | F | HC | 1/164 | N |

Leucine Rich Repeat-2 (LRR2), PLAT (Polycystin/Lipoxygenase/α-toxin), Poly-Glu (Poly-Glutamic acid region) TM2 (Transmembrane domain 2), *Fr* (*Fugu rubripes*), *Mm* (*Mus musculus*), *Hs (Homo Sapiens)*, LC (Level of amino acid Conservation), FC (Fully Conserved amino acid) were those that were identical in all three species compared, while amino acids with similar properties (i.e. belonging to the same amino acid class) were deemed to be "highly" conserved (HC) residues. NC (amino acid residues that were Not Conserved), N (Novel change, identified in this study), Rate=the number of times that the variant was observed in the study population (N=82, 164 chromosomes).

## *Supplementary Table 4. Analysis of Class II and Class III Sequencing Results*

| *ID* | *Amino acidic change* | | | | | *M&K* | *Conservation* | | | | *Family* | *Ref* | *Total # of variants.* | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Gene** | **cDNA** | **Protein** | ***Location*** | ***Domain*** | ***Matrix*** | ***Fr*** | **Mm** | **LC** | ***Rate*** | ***history*** | | **PKD1** | **PKD2** |
| JHU612 | *PKD1* | 1023C>A | A271D | Exon 5 | WSC | Path.H. | A | A | FC | 1/164 | No | N | 4 | 0 |
| | *PKD1* | 485A>G | A92T | Exon 2 | | Equal | F | A | HC | 1/164 | | N | | |
| JHU602 | *PKD1* | 1470A>G | Y420C | Exon 6 | C-LECT[a] | Path.H. | F | Y | HC | 1/164 | No | N | 25 | 1 |
| | *PKD1* | 4262C>T | R1351W | Exon 15 | PKDR7[a] | Path.H. | R | R | FC | 1/164 | | N | | |
| | *PKD1* | 8855T>A | W2882R | Exon 23 | | Path.H. | G | Q | NC | 1/164 | | N | | |
| | *PKD1* | 9109G>C | E2966D | Exon 24 | | Poly.H. | G | E | HC | 1/164 | | [6, 11-13] | | |
| JHU103 | *PKD1* | 1794A>G | Y528C | Exon 7 | C-LECT[a] | Path.H. | Y | Y | FC | 1/164 | Yes | N | 28 | 1 |
| | *PKD1* | 6036G>A | R1942H | Exon 15 | PKDR14 | Equal | R | R | FC | 1/164 | | N | | |
| JHU001 | *PKD1* | 2042C>T | R611W | Exon 9 | | Path.H. | R | R | FC | 1/164 | Yes | N | 6 | 0 |
| | *PKD1* | 8651G>A | G2814R | Exon 23 | REJ | Path.H. | A | G | HC | 6/164 | | [2, 14] | | |
| JHU411 | *PKD1* | 3351C>T | S1047L | Exon 13 | PKDR4[a] | Path.H. | M | S | HC | 1/164 | Yes | N | 60 | 1 |
| | *PKD1* | 6756A>G | Q2182R | Exon 15 | REJ | Path.H. | G | Q | HC | 2/164 | | [2, 14] | | |
| | *PKD2* | 634G>A | A190T | Exon 1 | | Equal | - | A | HC | 3/164[b] | | N | | |
| JHU100 | *PKD1* | 5793C>T | T1861I | Exon 15 | PKDR13[a] | Path.H. | T | S | HC | 1/164 | Yes | N | 8 | 1 |
| | *PKD1* | 6707C>T | R2166C | Exon 15 | REJ | Path.H. | P | R | HC | 1/164 | | N | | |
| | *PKD1* | 4229C>T | R1340W | Exon 15 | PKDR6[a] | Path.H. | H | H | FC | 3/164 | | [2] | | |
| JHU564 | *PKD1* | 10187G>C | G3326R | Exon 30 | TM3 | Path.H. | G | G | FC | 1/164 | Yes | N | 4 | 1 |
| | *PKD1* | 7116C>G | A2302G | Exon 15 | REJ | Equal | S | A | HC | 1/164 | | N | | |
| | *PKD1* | 10311A>G | I3367V | Exon 31 | | Poly. H. | I | V | HC | 1/164 | | N | | |
| JHU588 | *PKD1* | 7554T>C | L2448P | Exon 18 | REJ | Path.H. | L | L | FC | 1/164 | Yes | N | 39 | 0 |
| | *PKD1* | 4229C>T | R1340W | Exon 15 | PKDR6[a] | Path.H. | H | H | HC | 3/164 | | [2] | | |
| JHU603 | *PKD1* | 7757C>T | R2516C | Exon 19 | REJ | Path.H. | R | R | FC | 1/164 | Yes | N | 4 | 0 |
| JHU569 | *PKD1* | 8067T>C | L2619P | Exon 20 | REJ | Path.H. | L | L | FC | 1/164 | No | N | 22 | 2 |
| | *PKD1* | 8411C>A | P2734T | Exon 23 | REJ | Equal | P | P | FC | 1/164 | | [6] | | |
| | *PKD1* | 8415A>T | Q2735L | Exon 23 | REJ | Equal | S | Q | HC | 1/164 | | [6] | | |
| JHU597 | *PKD1* | 8138C>T | R2643C | Exon 21 | REJ | Path.H. | R | R | FC | 1/164 | No | N | 3 | 1 |
| JHU101 | *PKD1* | 8509C>T | R2767C | Exon 23 | REJ | Path.H. | R | R | FC | 1/164 | Yes | N | 4 | 2 |
| JHU109 | *PKD1* | 8522G>A | E2771K | Exon 23 | REJ | Path.H. | E | E | FC | 1/164 | Yes | [3, 6, 11] | 3 | 0 |
| JHU589 | *PKD1* | 8769T>C | F2853S | Exon 23 | | Path.H. | F | F | FC | 1/164 | Yes | [11, 15] | 22 | 2 |
| JHU 576 | *PKD1* | 10096C>A | N3295K | Exon 29 | TM2 | Path.H. | N | N | FC | 1/164 | Yes | N | 3 | 0 |
| JHU114 | *PKD1* | 12658C>T | R4149C | Exon 46 | | Path.H. | R | R | FC | 1/164 | Yes | N | 22 | 1 |
| | *PKD1* | 4229C>T | R1340W | Exon 15 | PKDR6[a] | Path.H. | R | R | HC | 3/164 | | [2] | | |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| JHU601B | *PKD1* | 9258A>G | Q3016R | Exon 25 | GPS | Path.H. | Q | Q | FC | 1/164 | Yes | [6, 11, 13, 15] | 43 | 1 |
| | *PKD1* | 2427A>G | Q739R | Exon 11 | | Path.H. | R | Q | HC | 11/164[c] | | [16] | | |
| *JHU565* | *PKD1* | *7476C>A* | *T2422K* | *Exon 18* | *REJ* | *Equal* | *T* | *T* | *FC* | *1/164* | *Yes* | *N* | *24* | *0* |
| | *PKD1* | *3527C>G* | *L1106V* | *Exon 15* | *PKDR4* | *Poly.H.* | *S* | *V* | *NC* | *1/164* | | *N* | | |
| | *PKD1* | *3713C>T* | *P1168S* | *Exon 15* | *PKDR5* | *Equal* | - | *P* | *HC* | *2/164[d]* | | [2] | | |
| *JHU570* | *PKD1* | 1947C>A | P579Q | Exon 9 | | Equal | P | P | FC | 1/164 | Yes | N | 5 | 1 |
| | *PKD1* | 2427A>G | Q739R | Exon 11 | | Path.H. | R | Q | HC | 11/164[c] | | [16] | | |
| *JHU575* | *PKD1* | 3312A>G | N1034S | Exon 13 | PKD R4 | Poly.H. | G | S | NC | 1/164 | No | N | 17 | 1 |
| *JHU178* | *PKD1* | 3713C>T | P1168S | Exon 15 | PKDR5 | Equal | - | P | HC | 2/164[d] | Yes | [2] | 2 | 1 |
| | *PKD2* | 634G>A | A190T | Exon 1 | | Equal | - | A | HC | 3/164[b] | | N | | |
| *JHU610* | *PKD2* | 634G>A | A190T | Exon 1 | | Equal | - | A | HC | 3/164[b] | No | N | 40 | 2 |
| *JHU617* | *PKD1* | 4391C>G | L1394V | Exon 15 | PKDR8[a] | Poly.H. | V | L | HC | 1/164 | Yes | N | 5 | 1 |
| | *PKD1* | 11040T>A | L3730Q | Exon 39 | | Equal | F | L | HC | 1/164 | | N | | |
| *JHU587* | *PKD1* | 840G>T | C210F | Exon 5 | | Equal | C | C | FC | 1/164 | No | N | 6 | 2 |
| | *PKD1* | 7197G>A | R2329Q | Exon 16 | REJ | Equal | E | R | HC | 1/164 | | N | | |
| | *PKD1* | 2427A>G | Q739R | Exon 11 | | Path.H. | R | Q | HC | 11/164[c] | | [16] | | |
| *JHU559* | *PKD1* | 351G>C | C47S | Exon 1 | LRR-N | Poly.H. | W | C | HC | 1/164 | Yes | N | 24 | 3 |
| | *PKD2* | 2464A>C | M800L | Exon 13 | | Poly.H. | - | M | HC | 1/164 | | [17] | | |
| *JHU606* | *PKD1* | 6809C>T | R2200C | Exon 15 | REJ | Path.H. | R | R | FC | 4/164[d] | No | [3] | 5 | 2 |
| *JHU584* | *PKD1* | 6809C>T | R2200C | Exon 15 | REJ | Path.H. | R | R | FC | 4/164[d] | No | [3] | 20 | 1 |
| *JHU106* | *PKD1* | 8651G>A | G2814R | Exon 23 | REJ | Path.H. | A | G | HC | 6/164 | Yes | [2, 6] | 4 | 1 |
| *JHU614* | *PKD1* | 4757G>A | A1516T | Exon 15 | PKDR9 | Equal | T | I | NC | 2/164 | No | N | 10 | 0 |
| | *PKD1* | 1973A>C | E586D | Exon 9 | | Poly H. | A | E | HC | 1/164 | | N | | |
| | *PKD1* | 2427A>G | Q739R | Exon 11 | | Path.H. | R | Q | HC | 11/164[c] | | [16] | | |
| *JHU102* | | | | | | | | | | | Yes | | 21 | 0 |
| *JHU598* | | | | | | | | | | | No | | 19 | 0 |
| *JHU616* | | | | | | | | | | | Yes | | 17 | 0 |
| *JHU110* | | | | | | | | | | | Yes | | 3 | 0 |
| *JHU113* | | | | | | | | | | | No | | 2 | 1 |
| *JHU615* | | | | | | | | | | | No | | 0 | 1 |

Only study participants with at least one predicted pathogenic missense change are underlined. The amino acid substitutions that meet the criteria for pathogenicity are shadowed in grey. An amino acid substitution was deemed to be pathogenic if it i) occurred at a fully or highly conserved amino acid residue, if it ii) was also predicted to have a higher pathogenic potential using the matrix of Miller and Kumar and if iii) it was absent in normals. Key: Disrupts consensus sequence of the domain (see Figure 2). Found in 3.2 % ([b]), 6.4 % ([c]), 1.7%

([d]) and 1.4% ([d]) of the normal population. Cell-wall integrity and Stress-response Component (WSC), C-type Lectin (C-LECT), Polycystic Kidney Disease Repeat # (PKD-R#), Receptor for Egg Jelly domain (REJ), Transmembrane # (TM#), GPCR proteolytic site (GPS), Leucine Rich Repeat (LRR), Novel change. LC (Level of amino acid Conservation), FC (Fully Conserved amino acid) were those that were identical in all three species compared, while amino acids with similar properties (i.e. belonging to the same amino acid class) were deemed to be "highly" conserved (HC) residues. NC (amino acid residues that were Not Conserved). Rate=the number of times that the variant was observed in the study population (N=82, 164 chromosomes).

***Supplementary Table 5. Missense Variants In Participants With Truncating Mutations, In frame Deletions/Insertions And Predicted Splicing Mutations.***

| | ***Mutations disease associated*** | | ***Amino acid changes highly pathogenic*** | | ***# of Changes per patient*** | |
|---|---|---|---|---|---|---|
| ***Pedigree*** | ***PKD1*** | ***PKD2*** | ***PKD1*** | ***PKD2*** | ***PKD1*** | ***PKD2*** |
| JHU605 | S91X | | | | 4 | 0 |
| JHU 567 | R1436X | | | | 24 | 0 |
| JHU108 | Y2265X | | Q739R[a] | | 5 | 1 |
| JHU563 | R2430X | | Q739R[a] | R807Q | 19 | 1 |
| JHU593 | Q2556X | | | | 3 | 2 |
| JHU083 | Q2686X | | | | 5 | 0 |
| JHU574 | E2810X | | G2814R | | 4 | 0 |
| JHU620 | W4011X | | | | 22 | 0 |
| JHU568 | W305 fsX | | W305C[b] | | 4 | 1 |
| JHU582 | P694 fsX | | | | 1 | 0 |
| JHU585 | A696 fsX | | | | 6 | 2 |
| JHU508 | V1718 fsX | | | | 5 | 2 |
| JHU613 | D2152 fsX | | E624K | | 21 | 0 |
| JHU611 | P2224 fsX | | | | 29 | 1 |
| JHU600 | P2975 fsX | | Q739R[a] | | 25 | 2 |
| JHU609 | I3109 fsX | | | | 41 | 1 |
| JHU579 | I3109 fsX | | G2814R | | 23 | 2 |
| JHU577 | F2834fsX | | Q739R[a] | | 4 | 1 |

| | | | | | | |
|---|---|---|---|---|---|---|
| JHU111 | N116 fsX | | R2200C[a] | | 7 | 1 |
| | | | S1619F | | | |
| JHU15 | R1672 fsX | | | | 5 | 1 |
| JHU599 | L3343 fsX | | *R1312Q* | | 20 | 1 |
| JHU104 | G3792 fsX | | | | 4 | 2 |
| JHU115 | N101del | | | | 20 | 0 |
| JHU107 | V546del | | R1142W | | 25 | 1 |
| JHU560 | ANS2894del | | | | 21 | 1 |
| JHU592 | K3232del | | | | 3 | 1 |
| JHU571 | L3287del | | | | 10 | 0 |
| JHU112 | V4129del | | S4053F | | 19 | 2 |
| JHU580 | IVS19+1G>T. | | G2814R | | 5 | 1 |
| JHU572 | IVS4+1G>A | | | S349P | 17 | 1 |
| JHU573 | IVS24+5G>C | | R2200C[a] | | 5 | 0 |
| JHU604 | IVS37-10C>A | | Q739R[a] | | 2 | 0 |
| | IVS24+28G> | | | | | |
| JHU590 | T | | | | 3 | 1 |
| JHU595 | IVS24+5G>C | | | | 16 | 2 |
| JHU578 | | R306X | | | 3 | 3 |
| JHU583 | | R306X | | | 5 | 1 |
| JHU607 | | R742X | | | 21 | 1 |
| JHU594 | | R872X | | | 22 | 3 |
| JHU566 | | R872X | | | 1 | 3 |

| | | | | |
|---|---|---|---|---|
| JHU608 | R872X | G2814R | 4 | 2 |
| JHU596 | 103insV | Q2182R | 35 | 1 |
| JHU416 | F605del | | 2 | 3 |
| JHU591 | 786fsX | | 4 | 2 |
| JHU562 | IVS7-1G>A | | 3 | 2 |
| | IVS8+5G> | | | |
| JHU105 | A | T1773I[b] | 3 | 2 |
| JHU116 | 720 fsX | Q739R[a] | 3 | 2 |
| JHU586 | 720 fsX | | 22 | 1 |

Missense variants listed in the table are predicted to be pathogenic according to the Matrix of Miller and Kumar (see text). Some of these variants are found in normal controls (a) or disrupt a consensus sequence for a *PKD1* domain (b).

***Supplementary Table 6. Polymorphisms Identified By Sequencing of PKD1 and PKD2***

| *ID#* | *Designation* | *cDNA Change (s)* | *Location* | *Domain* | *Frequency* | *Ref.* |
|---|---|---|---|---|---|---|
| ***PKD1 Polymorphisms.*** | | | | | | |
| - | T263S(H)* | 1004C>T | Exon 5 | | 2/164 | N |
| - | P572S(H)* | 1925C>T | Exon 8 | | 4/164 | [2] |
| - | M1092T(H)* | 3486T>C | Exon 14 | PKD R4 | 30/164 | [2] |
| - | W1399R(H)* | 4406T>G | Exon 15 | PKD R8 | 22/164 | [1, 2, 18] |
| - | V1943I(H)* | 6038G>A | Exon 15 | PKD R14 | 5/164 | [2] |
| - | E2548Q(H)* | 7853G>C | Exon 19 | REJ | 4/164 | [1] |
| - | H2638R(H)* | 8124A>G | Exon 21 | REJ | 32/164 | [1] |
| - | P2674S(H)* | 8231C>T | Exon 21 | REJ | 2/164 | [2, 6] |
| - | F3066L (H)* | 9407T>C | Exon 25 | | 38/164 | [6, 19] |
| - | V3408L(H)* | 10433G>C | Exon 33 | | 5/164 | N |
| - | A3511V(H)* | 10743C>T | Exon 35 | | 13/164 | [2, 6] |
| - | I4044V(H)* | 12341A>G | Exon 44 | TM10 | 42/164 | [2, 6, 12, 19, 20] |
| - | A4058V(H)* | 12386C>T | Exon 45 | | 12/164 | [2, 12] |
| **1** | * | 104C>T | Exon 1 | 5´UTR | 1/164 | N |
| **2** | * | 145C>T | Exon 1 | 5´UTR | 2/164 | N |
| **3** | * | 160C>T | Exon 1 | 5´UTR | 1/164 | N |
| **4** | * | 210C>T | Exon 1 | 5´UTR | 1/164 | N |
| **5** | L72L | 425C>T | Exon 1 | LRR1 | 2/164 | N |
| **6** | G109G | 538A>T | Exon 3 | LRR2 | 1/164 | N |
| **7** | S196S | 799C>T | Exon 5 | | 2/164 | N |
| **8** | A341A | 1234C>T | Exon 5 | PKD R1 | 5/164 | [6] |

| | | | | | | |
|---|---|---|---|---|---|---|
| **9** | L373L(H) | 1330T>C | Exon 5 | | 36/164 | [2, 4, 6] |
| **10** | G441G | 1534G>A | Exon 6 | C-LECT | 1/164 | N |
| **11** | H570H | 1921C>T | Exon 8 | | 1/164 | [2, 6] |
| **12** | IVS9+2del7* | | Intron 9 | | 12/164 | N |
| **13** | IVS9+2T>A** | | Intron 9 | | 1/164 | N |
| **14** | IVS9+28del7 (H)* | | Intron 9 | | 4/164 | [2] |
| **15** | ISV9-44G>C* | | Intron 9 | | 1/164 | [2] |
| **16** | IVS9-4A>G* | | Intron 9 | | 42/164 | [2] |
| **17** | IVS10-4 G>A$^{S1047L}$ | | Intron 10 | | 1/164 | N |
| **18** | P738P(H) | 2425C>G | Exon 11 | | 4/164 | N |
| **19** | A745A | 2448C>G | Exon 11 | | 1/164 | N |
| **20** | A898A | 2905A>C | Exon 11 | PKD R2 | 4/164 | [2, 14] |
| **21** | P900P | 2911G>A | Exon 11 | PKD R2 | 10/164 | [2, 18] |
| **22** | D910D | 2941C>T | Exon 11 | PKD R2 | 10/164 | [2, 18] |
| **23** | IVS11-5C>T* | | Intron 11 | | 2/164 | [2] |
| **24** | IVS11+23C>T(H)* | | Intron 11 | | 4/164 | N |
| **25** | IVS12-15C>T* | | Intron 12 | | 5/164 | N |
| **26** | G1021G(H) | 3274T>C | Exon 13 | PKD R4 | 30/164 | [2, 18] |
| **27** | L1037L | 3392A>G | Exon 13 | PKD R4 | 15/164 | [14] |
| **28** | E1061E | 3394G>A | Exon 14 | PKD R4 | 1/164 | N |
| **29** | P1076P | 3439G>A | Exon 14 | PKD R4 | 1/164 | N |
| **30** | A1124A | 3583C>T | Exon 15 | PKD R4 | 25/164 | [2, 14] |
| **31** | S1125S | 3586C>T | Exon 15 | PKD R5 | 25/164 | [2, 14] |
| **32** | F1163F | 3700C>T | Exon 15 | PKD R5 | 1/164 | N |
| **33** | T1171T | 3724C>G | Exon 15 | PKD R5 | 1/164 | N |

| | | | | | | |
|---|---|---|---|---|---|---|
| **34** | D1310D | 4141C>T | Exon 15 | PKD R7 | 1/164 | N |
| **35** | L1357L | 4282G>T | Exon 15 | PKD R7 | 1/164 | N |
| **36** | S1373S | 4330C>T | Exon 15 | PKD R7 | 1/164 | N |
| **37** | S1452S | 4567T>C | Exon 15 | PKD R8 | 1/164 | N |
| **38** | P1511P | 4744G>A | Exon 15 | PKD R9 | 1/164 | N |
| **39** | A1555A(H) | 4876A>C | Exon 15 | | 42/164 | [1, 14, 18] |
| **40** | T1558T | 4885G>A | Exon 15 | | 9/164 | [5] |
| **41** | S1603S | 5020C>T | Exon 15 | | 1/164 | N |
| **42** | T1724T(H) | 5383C>T | Exon 15 | PKD R12 | 40/164 | [2, 14, 16] |
| **43** | A1818A(H) | 5665G>A | Exon 15 | PKD R13 | 5/164 | [2, 14] |
| **44** | G1860G | 5791C>A | Exon 15 | PKD R13 | 1/164 | N |
| **45** | A1894A | 5893C>T | Exon 15 | PKD R14 | 1/164 | [2, 14] |
| **46** | L1921L | 5974G>A | Exon 15 | PKD R14 | 2/164 | [2, 14] |
| **47** | V2026V | 6289C>T | Exon 15 | PKD R15 | 1/164 | N |
| **48** | R2121R | 6574C>T | Exon 15 | PKD R16 | 1/164 | N |
| **49** | T2180T | 6751C>T | Exon 15 | REJ | 1/164 | N |
| **50** | A2202A | 6817G>A | Exon 15 | REJ | 1/164 | N |
| **51** | V2257V | 6982G>A | Exon 15 | REJ | 1/164 | N |
| **52** | G2309G | 7138C>T | Exon 16 | REJ | 4/164 | [2, 14] |
| **53** | IVS16+10 G>A* | | Intron 16 | REJ | 1/164 | N |
| **54** | R2359R | 7289G>C | Exon 17 | REJ | 3/164 | N |
| **55** | L2389L(H) | 7376T>C | Exon 17 | REJ | 46/164 | [1, 2, 5, 14] |
| **56** | G2425G | 7486C>T | Exon 18 | REJ | 1/164 | N |
| **57** | L2481L(H) | 7652C>T | Exon 18 | REJ | 39/164 | [1, 2] |
| **58** | IVS19+24 C>A* | | Intron 19 | REJ | 2/164 | N |

| | | | | | | |
|---|---|---|---|---|---|---|
| **59** | L2570L(H) | 7919T>C | Exon 20 | REJ | 31/164 | [1, 14] |
| **60** | ISV20-16C>G$^{C47S, L3720Q}$ | | Intron20 | REJ | 2/164 | N |
| **61** | T2708M | 8334C>T | Exon 22 | REJ | 1/164 | [2, 6] |
| **62** | IVS22+8G>A(H)* | | Intron 22 | REJ | 1/164 | [1, 2] |
| **63** | S2729S | 8398G>A | Exon 23 | REJ | 2/164 | N |
| **64** | A2749A | 8458G>A | Exon 23 | REJ | 1/164 | N |
| **65** | S2766S | 8509C>T | Exon 23 | REJ | 1/164 | [21] |
| **66** | D2789D | 8578C>T | Exon 23 | REJ | 2/164 | N |
| **67** | S2813S | 8650C>T | Exon 23 | REJ | 2/164 | [2, 6, 11] |
| **68** | S2893S | 8890C>G | Exon 23 | | 2/164 | [6] |
| **69** | A2971A(H) | 9124T>C | Exon 24 | | 2/164 | N |
| **70** | IVS24-20G>A(H)* | | Intron 24 | | 3/164 | N |
| **71** | IVS24-17A>G(H)* | | Intron 24 | | 6/164 | N |
| **72** | IVS24+17A>G* | | Intron 24 | | 32/164 | N |
| **73** | S3007S | 9232C>T | Exon 25 | | 1/164 | N |
| **74** | V3065V(H) | 9406G>C | Exon 25 | | 38/164 | [11] |
| **75** | V3090V | 9481C>T | Exon 26 | TM1 | 3/164 | N |
| **76** | P3110P(H) | 9543T>C | Exon 26 | | 37/164 | [15] |
| **77** | IVS26+76C>A$^{L2617P}$ | | Intron26 | | 1/164 | N |
| **78** | IVS27-13T>C(H)* | | Intron27 | | 15/164 | [6] |
| **79** | T3223T | 9880G>A | Exon 28 | PLAT | 2/164 | [2, 6, 15] |
| **80** | S3265S | 10006C>T | Exon 29 | | 1/164 | N |
| **81** | IVS29-4C>T* | | Intron29 | | 1/164 | N |
| **82** | A3455A | 10576C>T | Exon 34 | | 1/164 | N |
| **83** | L3589L | 10976C>T | Exon 36 | TM5 | 5/164 | [22] |

| | | | | | | |
|---|---|---|---|---|---|---|
| **84** | IVS37-4C>T $^{Q3016R}$ | | Intron 37 | | 1/164 | N |
| **85** | IVS38+11G>A* | | Intron 38 | | 4/164 | N |
| **86** | R3752R | 11385C>A | Exon 39 | PC | 1/164 | N |
| **87** | L3753L | 11465G>C | Exon 39 | PC | 1/164 | N |
| **88** | IVS39-25del72bp* | | Intron 39 | | 1/164 | [6, 23] |
| **89** | IVS41+3insGGG* | | Intron 41 | | 2/164 | [2] |
| **90** | IVS41-11C>T*R2516C | C>T | Intron 41 | | 2/164 | N |
| **91** | S3893S(H) | 11890C>T | Exon 42 | | 3/164 | [2] |
| **92** | IVS43+42C>A* | | Intron 43 | | 6/164 | N |
| **93** | R3971R | 12124C>T | Exon 43 | | 3/164 | N |
| **94** | L4025L | 12286C>T | Exon 44 | | 1/164 | N |
| **95** | L4035L | 12316C>T | Exon 44 | TM10 | 1/164 | N |
| **96** | IVS44+22delG* | | Intron44 | | 4/164 | N |
| **97** | L4089L | 12478C>G | Exon 45 | TM11 | 1/164 | N |
| **98** | A4091A(H) | 12484A>G | Exon 45 | TM11 | 43/164 | [2, 6, 19, 23] |
| **99** | L4136L(H) | 12617C>T | Exon 45 | | 13/164 | [2, 20] |
| **100** | V4152V | 12667C>T | Exon 46 | | 2/164 | N |
| **101** | P4161P | 12696C>A | Exon 46 | | 1/164 | N |
| **102** | S4189S | 12778C>T | Exon 46 | | 1/164 | N |
| **103** | P4209P(H) | 12838T>C | Exon 46 | | 40/164 | [2, 6] |
| **104** | L4221L | 12874C>T | Exon 46 | CC | 1/164 | N |
| **105** | A4255A | 12978C>T | Exon 46 | | 1/164 | N |
| **106** | | 13135G>A | 3´UTR | | 2/164 | [2] |
| ***PKD2 Polymorphisms.*** | | | | | | |
| **-** | R28P(H)* | 149C>T | Exon 1 | | 50/164 | [2, 12, 24] |

| | | | | | |
|---|---|---|---|---|---|
| **107** | R60R | 246G>A | Exon 1 | 1/164 | N |
| **108** | G140G(H) | 486G>A | Exon 1 | 22/164 | N |
| **109** | IVS6-4C>T $^{C47S}$ | | Intron 6 | 1/164 | N |
| **110** | L539L | 1683G>C | Exon 7 | 1/164 | N |

Polymorphisms were defined as sequence variants that were 1) not predicted to alter an amino acid, 2) intronic changes associated with truncating mutations, 3) polymorphisms reported by others, 4) missense changes associated with truncating mutations and 5) changes in the 3' UTR of unknown significance. Some polymorphisms were found in homozygosity (H). Polycystic Kidney Disease Repeat # (PKD-R#), Receptor for Egg Jelly domain (REJ), Transmembrane # (TM#), 5' Untranslated region (5'UTR), Leucine Rich Repeat# (LRR#), C-type Lectin (C-LECT), Cell-wall integrity and Stress-response Component (WSC), GPCR proteolytic site (GPS), Coiled Coil (CC), PM (Polycystin Motif), Novel change (N). Polymorphisms observed in patients with Class I change in PKD1 (*) or PKD2 (**), Class II missense amino acid substitutions ($^{superscript}$) are indicated. Rate=the number of times that the variant was observed in the study population (N=82, 164 chromosomes).